receptor IGF1R serves as a prognostic marker to predict the unfordable outcomes of CRC patients (IDDF2021-ABS-0173 Figure 2A, IDDF2021-ABS-0173 Figure 2B, IDDF2021-ABS-0173 Figure 2C, IDDF2021-ABS-0173 Figure 2D, IDDF2021-ABS-0173 Figure 2E, IDDF2021-ABS-0173 Figure 2F, IDDF2021-ABS-0173 Figure 2G, IDDF2021-ABS-0173 Figure 2H, IDDF2021-ABS-0173 Figure 2I, IDDF2021-ABS-0173 Figure 2J, IDDF2021-ABS-0173 Figure 2K). Apart from Akt-mTOR pathway, RNA-seq analysis revealed that YAP1 signaling serves as a prominent downstream modulator to mediate oncogenic signaling of IGF2-IGF1R. By single-cell RNA sequencing (scRNA-seq), IGF2 was found to be predominantly secreted by CAFs, while IGF1R-YAP1 was averagely distributed in CAFs and cancer cells. When stimulating IGF1R by rhIGF2, F-actin remodeling, nuclear accumulation of YAP1, and overexpression of YAP1 targets were observed, but these effects were attenuated by either IGF1R depletion or Picropodophyllin (IGF1R inhibitor) administration (IDDF2021-ABS-0173 Figure 3A, IDDF2021-ABS-0173 Figure 3B, IDDF2021-ABS-0173 Figure 3C, IDDF2021-ABS-0173 Figure 3D, IDDF2021-ABS-0173 Figure 3E, IDDF2021-ABS-0173 Figure 3F, IDDF2021-ABS-0173 Figure 3G, IDDF2021-ABS-0173 Figure 3H, IDDF2021-ABS-0173 Figure 3I, IDDF2021-ABS-0173 Figure 3J, IDDF2021-ABS-0173 Figure 3K, IDDF2021-ABS-0173 Figure 3L, IDDF2021-ABS-0173 Figure 3M, IDDF2021-ABS-0173 Figure 3N, IDDF2021-ABS-0173 Figure 3O). By in vivo studies, we found that co-targeting IGF1R and YAP1 by Picropodophyllin and Verteporfin (YAP1 inhibitor) achieved the anti-tumor effects in subcutaneous xenograft and orthotopic implantation models. The synergistic effects were also validated in a patient-derived organoid with IGF1R-YAP1 co-upregulation (IDDF2021-ABS-0173 Figure 4A, IDDF2021-ABS-0173 Figure 4B, IDDF2021-ABS-0173 Figure 4C, IDDF2021-ABS-0173 Figure 4D, IDDF2021-ABS-0173 Figure 4E, IDDF2021-ABS-0173 Figure 4F, IDDF2021-ABS-0173 Figure 4G, IDDF2021-ABS-0173 Figure 4H, IDDF2021-ABS-0173 Figure 4I, IDDF2021-ABS-0173 Figure 4J).

Conclusions This study revealed the promoting role of CAFs in CRC progression. The findings highlight the translational potential of IGF2-IGF1R-YAP1 axis, which may serve as a prognostic biomarker and therapeutic target for CRC.

SARS-COV-2 ACTIVATES LUNG EPITHELIAL CELL PROINFLAMMATORY SIGNALING AND LEADS TO IMMUNE DYSREGULATION IN COVID-19 PATIENTS

Weixin Liu,1,2 Huarong Chen,3 Yifei Wang,2 Dabin Liu,1 Liuyang Zhao,1 Jun Yu.1 Institute of Digestive Disease and Department of Medicine and Therapeutics, State Key laboratory of Digestive Disease, Li Ka Shing Institute of Health Sciences, CUHK Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong;2 Department of Anaesthesia and Intensive Care and Peter Hung Pain Research Institute, The Chinese University of Hong Kong, Hong Kong, China;3Department of Anatomical and Cellular Pathology, State Key Laboratory of Translational Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, SARR, PR China

10.1136/gutjnl-2021-IDDF.5
ALTERED GUT METABOLITES AND TURNING IMMUNOLOGICALLY COLD

A6

Methods We analyzed single-cell RNA sequencing (scRNA-seq) data of bronchoalveolar lavage fluid (BALF) samples from 10 healthy donors, 6 severe COVID-19 patients and 3 mild recovered patients. The expressions of SARS-CoV-2 receptors (ACE2 and TMPRSS2) were examined among different cell types. The immune cells infiltration patterns, their expression profiles, and interplays between immune cells and SARS-CoV-2 target cells were further investigated.

Results Compared to healthy controls, ACE2 and TMPRSS2 expressions were significantly higher in lung epithelial cells of COVID-19 patients, in particular club and ciliated cells. SARS-CoV-2 activated pro-inflammatory genes and interferon/ cytokine signaling in these cells. In severe COVID-19 patients, significantly higher neutrophil, but lower macrophage in the lung was observed along with markedly increased cytokines expression compared with healthy controls and mild patients. By contrast, neutrophil and macrophage returned to normal level whilst more T and NK cells accumulation were observed in mild patients. Moreover, SARS-CoV-2 infection altered the community interplays of lung epithelial and immune cells: interactions between the club and immune cells were higher in COVID-19 patients compared to healthy donors; on the other hand, immune-immune cells interactions appeared the strongest in mild patients.

Conclusions SARS-CoV-2 could infect lung epithelium, alter communication patterns between lung epithelial cells and immune system, and drive dysregulated host immune response in COVID-19 patients.

ALTERED GUT METABOLITES AND BACTERIAL INTERACTIONS ARE IMPLICATED IN COLORECTAL CARCINOGENESIS AND CAN DETECT PRECANCEROUS AND CANCEROUS LESIONS

IDDF2021-ABS-0210

Background The outbreak of Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection has become a global health emergency. We aim to decipher SARS-CoV-2 infected cell types, the consequent host immune response and their interplay in the lung of COVID-19 patients.

Methods We performed metabolomics by gas chromatography mass spectrometry to detect gut microbiota metabolites and their linkage to CRC. We aim to determine gut microbiota-associated metabolites and bacteria were altered across CRC stages; correlation positive with differentially expressed genes were used to identify metabolites and bacterial markers discriminating CRC stages. Associations among CRC-associated metabolites and bacteria were estimated with zero-inflated negative binomial regressions analysis.

Results Principal component analysis and partial least squares-discriminant analysis showed differences in the gut metabolite profiles among CRC, CRA and NC groups. Norvaline and myristic acid showed increasing trends from NC, through CRA, to CRC. CRC-associated metabolites were enriched in branched-chain amino acids and aminomalonyl-tRNA biosynthesis pathways. Twenty metabolites classified CRC from NC subjects with an area under the curve (AUC) of 0.80, and CRC from CRA with AUC of 0.79. Combinations of metabolites and bacterial markers improved the diagnostic performances (CRC vs NC, AUC: 0.94; CRC vs CRA, AUC 0.92; CRA vs NC, AUC: 0.86), indicating a potential for early diagnosis of colorectal neoplasia. Moreover, relationships among CRC-associated metabolites and bacteria were altered across CRC stages; certain associations exhibited increasing or decreasing strengths while some were reversed from negative to positive or vice versa.

Conclusions Gut metabolites are altered in colorectal carcinogenesis. The combination of metabolites and bacterial species can increase the chance of a non-invasive diagnosis of colorectal neoplasia.

Basic Hepatology

IDDF2021-ABS-0145 TURNING IMMUNOLOGICALLY COLD TUMORS INTO HOT ONES BY ACTIVATING HEPATOMA-INTRINSIC FADD/NF-KB/CC5 PATHWAY

Jiahuan Lu*, Jing Wang, Yalin Tu, Weiqing Yang, Wenshu Tang, Zheyun Xiong, Alfred Sz Lok Cheng, Anthony Wang-Hung Chan, Ka-Fai To. Chinese University of Hongkong, Hong Kong

Background Lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) as a distinct variant of HCC displayed immunologically hot tumor features with prominent tumor-infiltrating CD8+$T$ lymphocytes (TILs). Our whole exosome sequencing data found an increased prevalence of chromosome 11q13.3 amplification in LEL-HCC, in which contains fas-associated death domain (FADD) that displayed a strongest positive correlation with differentially expressed genes function in TIL migration. We hence aim to elucidate the functional roles and molecular mechanisms of hepatoma-intrinsic FADD in regulating TIL abundance in general HCC patients.

Methods FADD-overexpressed HepG2 (FADD-oe) and FADD-knockdown huh7 cells (FADD-kd) were constructed to investigate cell growth rate by colony formation and MTS assay in vitro, subcutaneous tumor in immunodeficient nude and NOD/SCID mice in vivo. A co-culture model of human peripheral blood-derived-CD8+$T$ cells and HepG2-oe or Huh7-kd in vitro, T cell adoptive transfer and humanized mice models in vivo were used to detect T migration preference. The downstream functional chemokines and molecular pathways controlled by FADD were determined by RT-qPCR, ELISA, western blot as well as gene modulation assays. Finally,